REMARKS

The following remarks and accompanying declarations, supplemental information disclosure statement and references are submitted in response to the Office Action mailed May 4, 2006. Currently Claims 38-60 and 73-81 are pending, with Claims 40-43, 55-59, 61-72 and 77-80 having been withdrawn and all other claims standing rejected. Applicants have cancelled withdrawn Claims 61-72, directed to a nonelected invention, without prejudice to the potential refiling of such claims in a divisional application. All other withdrawn claims are directed to nonelected species and depend from generic claims that Applicants submit to be in condition for allowance, and thus have been maintained. Claim 53 has been amended.

In view of the above amendment, the following remarks, and the attached evidence in support of patentability, reconsideration is respectfully requested.

I. Information Disclosure Statements

In the Office Action of May 4, 2006, the Examiner kindly acknowledged receipt of a supplemental information disclosure received by the PTO on January 27, 2006. However, the single reference listed on the Citation of Information form (PTO form 1449) was inadvertently not initialed. To clarify the record, the Examiner is respectfully requested to initial and return that form (duplicate copy enclosed), as well as the Citation of Information form attached to the new supplemental information disclosure statement submitted herewith in keeping with Applicants continuing duty of disclosure.

II. Rejection Under 35 USC § 112, First Paragraph

Claims 38, 39, 44-54, 59, 60, 73-76 and 81 stand rejected for a perceived lack of enablement under the first paragraph of 35 USC § 112. The Office Action acknowledges that the specification is enabling for specific catabolic inhibitors such as MAPK inhibitors and interleukins, but states the view that the specification is not reasonably enabling for the broader

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

categories of catabolic inhibitors and anabolic compounds. Applicants respectfully traverse this rejection.

A. Enablement Standards - No *Prima Facie* Case

A lack of enablement rejection under Section 112, first paragraph, is appropriate only where the written description fails to teach those in the art how to make and use the invention as broadly as claimed without undue experimentation. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). The enablement requirement is satisfied as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). In the instant application, numerous examples of anabolic chondroprotective agents and inhibitors of cartilage catabolism are disclosed, as acknowledged in the Office Action. The concern set forth in the Office Action, as understood by the undersigned attorney, is with the breadth of the catabolic inhibitor and anabolic agent "genus" terms. First, it is noted that not every anabolic agent or catabolic inhibitor is claimed. Instead, referring to independent Claims 38 and 73, the claimed methods recite the use of "anabolic chondroprotective agents" and "inhibitors of cartilage catabolism." Thus the claimed agents are limited to those that exhibit catabolic inhibitory or anabolic effects in the joint.

Moreover, enabling the full scope of a claim does not necessarily require enabling every embodiment within the claim. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). It is also well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. Rather, it is required that there be a significant disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

The present specification discloses many species of catabolic inhibitory agents and anabolic agents that support the full breadth of the claimed genus. Such agents are *individually* well known and characterized by those of skill in the art, as evidenced by the extensive disclosure concerning representative classes of agents set forth in the specification. The claimed invention is not directed to new and poorly characterized biological targets. The novelty and inventiveness of the claimed invention lies not in the individual inhibitors of cartilage catabolism or anabolic chondroprotective agents, but rather in the claimed methods of administering combinations of such agents.

When rejecting a claim under Section 112, the USPTO bears the initial burden of asserting a *prima facie* case explaining why the scope of protection provided by that claim is not enabled by the specification. *In re Marzocchi*, 169 U.S.P.Q. 367 (1971). This *prima facie* case must include "sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

Based on the extensive disclosure contained in the specification regarding suitable species of anabolic chondroprotective agents and inhibitors of cartilage catabolism, Applicants submit that the Office Action fails to set forth a *prima facie* case of nonenablement. However, to expedite prosecution of the application, Applicants provide evidence and rationale clearly establishing that the present claims are enabled even if a *prima facie* case is assumed to have been established (which Applicants assert not to be the case).

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

B. No Undue Experimentation

The scope of what is enabled in an application is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation. *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999), citing *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) An application satisfies the enablement requirement only if one skilled in the art, after reading the disclosure, could practice the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). As noted by the Examiner, the Federal Circuit has stated that the following factors are relevant to determine if a specification is enabled for a particular claim: (1) the breadth of the claim; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Before addressing these factors individually, Applicants provide evidence as to the level of knowledge in the art. Applicants submit herewith three declarations from skilled researchers and practitioners in the fields of osteoarthritis, rheumatoid arthritis and other joint diseases. The declarations were originally drafted and submitted in a corresponding European Patent Application (No. 00947581.5) that is based on the same International PCT Application Number PCT/US00/19864 as the instant US Patent Application, which included corresponding claims to those currently pending. While having been submitted in the EP Application, and found sufficient by the EPO to permit the EPO to search and examine the full scope of the claims, each declaration also includes an averment in conformity with 18 USC § 1001. Each of these experts

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

is highly regarded in the relevant scientific community, with their work having been widely published in peer-reviewed journals.

- Steven B. Abramson, M.D. is a Professor of Medicine and Pathology, and Chairman of the Departments of Rheumatology and Medicine, at the Hospital for Joint Diseases, New York University School of Medicine. (Exhibit A).
- Steven R. Goldring, M.D., at the time of making his declaration, was a Professor of Medicine at Harvard Medical School, Director of Research at New England Baptist Bone and Joint Institute, and Chief of Rheumatology at New England Baptist Hospital, Beth Israel Deaconess Medical Center and New England Deaconess Hospital. Dr. Steven Goldring is currently the Chief Scientific Officer at the Hospital for Special Surgery, New York, New York. (Exhibit B).
- Mary B. Goldring, Ph.D., at the time of making her declaration, was an Associate Professor of Medicine (cell biology) at the Beth Israel Deaconess Medical Center and Harvard Medical School, and a Senior Scientist at the New England Baptist Bone & Joint Institute. Dr. Mary Goldring is now also at the Hospital for Special Surgery, New York, New York. (Included in Exhibit B).
- Martin Lotz, M.D. is a Research Professor, Department of Medicine, University of California, San Diego, and Professor, Department of Molecular and Experimental Medicine, as well as Head, Division of Arthritis Research, The Scripps Research Institute. (Exhibit C).

The relevant potions of the CVs for these declarants, thought leaders in their fields of research, are attached to their respective declarations. Each declarant is well positioned in his or her own right to determine the state of knowledge in the relevant art field as of the earliest

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

priority date for the instant application, as well as the degree of experimentation that would be required to practice the scope of the claimed invention. Together, they unquestionably are able to address these issues.

The Applicants requested each declarant to state his or her view regarding the definitiveness of terms used in the pending independent claims. Each declarant states unequivocally that the term "chondroprotective agent" or "chondroprotection" was widely used in the literature. The term has been used since at least the mid 1980's. Dr. Abramson Declaration, p. 2. Dr. Steven Goldring and Dr. Mary Goldring report that the terms "chondroprotection" and "chondroprotective" had been used in at least 156 publications prior to the priority date of the instant application. Drs. Goldring Declaration, p. 2. The terms "anabolic" and "catabolic" in the context of cartilage metabolism and joint disease were familiar to anyone in broad clinical fields such as general medicine, internal medicine, rheumatology and orthopedics. Dr. Lotz Declaration, p. 2.

The term "inhibitor of cartilage catabolism" is likewise well described and characterized in the literature, and recognized by those of skill in the art. Dr. Abramson Declaration, p. 2; Drs. Goldring Declaration, p. 3; Dr. Lotz Declaration, p. 2. The term "anabolic chondroprotective agent" is also well described and characterized in the literature, and recognized by those of skill in the art. Dr. Abramson Declaration, p. 2; Drs. Goldring Declaration, p. 4; Dr. Lotz Declaration, p. 2.

Each declarant also sets forth their view that one of skill in the art would readily be able to tell whether a given agent is an inhibitor of cartilage catabolism or an anabolic chondroprotective agent. Known methods, assays, standards and/or tests to readily make this determination are identified by each of the declarants. Dr. Abramson Declaration, pp. 2-3; Drs. Goldring Declaration, pp. 3-5; Dr. Lotz Declaration, pp. 2-3. It is clear that this

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

determination would not require inventive activity or place an undue experimentation burden on one of skill in the art seeking to practice the invention.

C. Application of *In re Wands* Factors Establishes that Claims are Enabled

Applicants respectfully submit that a careful consideration of the factors set forth by the Federal Circuit in *In re Wands* for evaluating enablement, in view of the evidence submitted herewith and described above, clearly establishes that the pending claims are fully enabled.

1. Breadth of Claims: The claimed methods of the present invention are directed to the use of combinations of chondroprotective agents including at least an anabolic chondroprotective agent and an inhibitor of cartilage catabolism. While relatively broad, the claims are focused on agents that effect cartilage and cartilage protection, and the nature of the agents are well known and readily understood by those of skill in the art as evidenced by the expert declarations of Exhibits A-C.

2. Nature of the Invention: For claims directed to a specific therapeutic use, evidence of enablement should be sufficient to convince one skilled in the art that the method would have some beneficial therapeutic effect. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In the instant case, the individual agents utilized in the claimed combination are well recognized as having beneficial effect when conventionally administered. The agents used in the claimed combinations modulate well characterized pathways, and are not directed to uncharacterized targets in which therapeutic effect would be in doubt.

3. State of the Prior Art: The declarations of Exhibits A-C establish that, at the time of filing of the priority application on which the instant application is based, the prior art was well developed with regard to the identification of anabolic chondroprotective agents and inhibitors of cartilage catabolism. "A patent disclosure need not enable information within the knowledge of an ordinary skilled artisan, thus, a patentee preferably omits from the disclosure any routine

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

technology that is well known at the time of application." *Chiron Corp v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004) *cert denied*, 125 S. Ct. 870 (2005), quoting *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986). The prior art knowledge of chondroprotective agents and assays to readily determine the same, together with the disclosure in the instant specification, clearly permits the ready making and using of the claimed invention.

4. Level of One of Ordinary Skill: The USPTO considers the level of skill in the art of molecular biology, which is applicable to the instant invention, to be "relatively high." *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

5. Level of Predictability in the Art: The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. *Bayer AG v. Schein Pharmaceuticals, Inc.*, 301 F.3d 1306, 1314 (Fed. Cir. 2002). Again, Applicants note that the individual agents used in the novel claimed inventions of the present application are well characterized.

6. Direction Provided by the Inventor: In the area of biotechnology, a key issue that can arise is whether the starting materials necessary to make the invention are available, or are available only after extensive screening. *In re Ghiron*, 169 U.S.P.Q. 723 (C.C.P.A. 1971); M.P.E.P. § 2164.01(b). In this case, the specification discloses a plethora of established anabolic chondroprotective agents and inhibitors of cartilage catabolism that can be selected for practice of the claimed methods.

7. Working Examples: The present specification discloses a number of prophetic examples. While the lack of a working example is a factor to be considered, it is well established that a claimed invention that has been disclosed is not also required to have been physically

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

made to satisfy the enablement requirement. *Elan Pharm. Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003).

8. Quantity of Experimentation Needed: Numerous examples of chondroprotective agents are disclosed in the instant specification. Other chondroprotective agents can be identified using well established assays. See, e.g., Drs. Goldring Declaration, pages 3-5. The time required and difficulty of experiments required to practice an invention is not determinative of undue experimentation if the experiments are merely routine. *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The declarations of Exhibits A-C establish that routine assays are all that is required to identify additional agents for use in the claimed invention.

In determining whether undue experimentation is required, the Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 8 U.S.P.Q.2d at 1404. The *Wands* factors are "illustrative, not mandatory" and all eight factors need not be reviewed in determining whether a disclosure is enabling; what is relevant depends on the facts. *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). Considering the above factors in view of the substantial disclosure contained in the instant specification, the well established nature of the individual agents utilized in the claimed novel combinations, the high level of skill in the art, the extensive prior art knowledge applicable to the identification of individual chondroprotective agents, and the availability of routine assays for identifying agents, as supported by the declarations of Exhibits A-C, Applicants respectfully submit that the claimed invention is fully enabled.

III. Rejection Under 35 USC § 112, Second Paragraph

Claim 53 stands rejected as being indefinite under the second paragraph of 35 USC § 112. The clause regarding fragments, deletions, etc. that was of concern to the Examiner has

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

been deleted from the claim, with the intent and understanding that the claim terms will still be construed in view of the corresponding disclosure included in the specification. Applicants submit that this rejection has been overcome.

IV. Rejection under 35 USC § 103

Claims 38, 39, 44-54, 59, 60, 73-76 and 81 stand rejected under 35 USC § 103 based on the hypothetical combination of US Patent 6,096,728 to Collins et al. and US Patent 5,206,023 to Hunziker. Collins '728 was cited in the Office Action for the disclosure of the administration of an IL-1 inhibitor with additional agents such as MAPK inhibitors or anti-inflammatory agents for the treatment of osteoarthritis, psoriatic arthritis and/or rheumatoid arthritis. However, as acknowledged in the Office Action, Collins '728 does not disclose the inclusion of a growth factor or other anabolic chondroprotective agent with the IL-1 inhibitor. Hunziker '023 was cited for the disclosure of fibroblast growth factors (FGF) to treat defects in cartilage. Hunziker '023 does not disclose the administration of catabolic inhibitory agents together with anabolic promoting agents. Rather, Hunziker '023 is solely directed to inducing repair and regeneration (Column 3, lines 27-31). Applicants respectfully traverse this rejection.

Before addressing the rejection further, Applicants briefly reprise the overview of the invention previously submitted with the prior response. Independent Claim 38 is directed to a method of inhibiting cartilage degradation in a joint of a patient, by delivering a composition including chondroprotective agents in solution. The composition includes a therapeutically effective amount of a first chondroprotective agent that is an anabolic chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent that is an inhibitor of cartilage catabolism. This composition is delivered locally to the joint. The method of independent Claim 73 is similar to that of independent claim 38, but additionally calls for the composition to be delivered to the joint within an acute phase following trauma to the joint.

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

A. No *Prima Facie* Case of Obviousness

Applicants again respectfully submit that the hypothetical combination of Collins '728 and Hunziker '023 does not result in a *prima facie* case of obviousness. The Office Action looks to the disclosure of Hunziker '023 for a motivation to combine the catabolic inhibitory agents of the Collins '728 reference with the anabolic agents of the Hunziker '023 reference. Specifically, the Office Action states with regard to Hunziker '023 that "the compounds recited include tumor necrosis factors (TNF alphas) described by applicant as inhibitors of cartilage catabolism and TGF-betas, described by applicants as anabolic agents." Applicants respectfully submit that either the reference or the present invention has been misunderstood. Hunziker '023 does disclose the use of "tumor necrosis factors (e.g., TNF-α, TNF-β)" as chemotactic agents useful in the compositions and methods of the disclosed invention for "attracting repair cells." However, these are not inhibitors of cartilage catabolism as presently claimed, which include *antagonists* of TNF-α. In other words, Hunziker '023 discloses the use of TNF- α, while the present invention encompasses the use of inhibitors of TNF- α. Thus, Hunziker '023 actually teaches away from the present invention. Hunziker '023 discloses only combinations of anabolic agents, and optionally includes the inflammatory mediator TNF- α; Hunziker '023 does not provide motivation for combining anabolic agents with inhibitors of cartilage catabolism.

Unlike either Collins '728 or Hunziker '023, the present invention provides a method for inhibiting cartilage degradation that addresses *both* sides of the cartilage matrix homeostasis equation: an anabolic chondroprotective agent to promote cartilage synthesis together with an inhibitor of cartilage catabolism to inhibit cartilage break-down. Conventional approaches for the treatment of cartilage disorders rely on the administration of inhibitors of cartilage catabolism, such as (TNF-α) inhibitors (i.e., antagonists) or interleukin–1 (IL-1) inhibitors. Separately, growth factors are also being developed for use as anabolic promoting agents in

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

treating cartilage disorders. However, as noted in the previous response, these two distinct, parallel paths have conventionally been followed *separately* as *alternative* approaches, and those of skill in the art would not be motivated to combine these approaches.

This point is buttressed by the declarations of Drs. Abramson, M. Goldring, S. Goldring and Lotz attached hereto as Exhibits A-C, which attest to the fact that inhibitors of cartilage catabolism (e.g., MMP inhibitors, IL-1 antagonists) were well known in the relevant scientific community prior to the present invention. *See, e.g.*, Dr. Abramson Declaration, p. 2. Likewise, cartilage anabolic agents (e.g., TGF-β, BMPs) were well known in the same scientific community prior to the present invention. *See, e.g.*, Drs. Goldring Declaration, p. 3. Despite this contemporaneous knowledge for years prior to the present invention, therapies and research focused either only on the administration of catabolic inhibitors, or only on the potential administration of anabolic agents. *See, e.g.*, Dr. Lotz Declaration, p. 3, Drs. Goldring Declaration, p. 5. The scientific and medical community did not at the time recognize that medicaments should include both a catabolic inhibitor and an anabolic agent. Further, those of skill in the art failed to recognize the unique advantages of local administration of combinations of catabolic inhibitory agents with cartilage anabolic agents. *See, e.g.*, Drs. Goldring Declaration, p. 5. This was despite the fact that both approaches were being contemporaneously discussed for years in the same venues, such as at the same scientific workshop. Drs. Goldring Declaration, p. 3.

B. Long-term Failure to Recognize Invention

The declarations addressed above make clear that those of skill in the art would not have previously been motivated to combine the Collins '728 and Hunziker '023 approaches. In addition to there being no *prima facie* case of obviousness, the long-term failure of those of skill in the art to recognize the present invention, even when presented with two of its component

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

parts (Dr. Lotz Declaration, p. 3, Drs. Goldring Declaration, p. 5) is a secondary factor that strongly supports the inventiveness of the present claimed invention.

C. Advantages of Local Delivery

As noted above, conventional clinical approaches to the treatment of cartilage degenerative disorders, such as rheumatoid arthritis and osteoarthritis, rely upon agents that act to inhibit cartilage degradation, e.g., interleukin-1 (IL-1) receptor antagonists and tumor necrosis factor-α (TNF-α) receptor antagonists for rheumatoid arthritis, and cyclooxygenase-2 (COX-2) inhibitors for osteoarthritis. Such therapeutics are conventionally administered systemically, and as such may be associated with undesirable systemic side effects.

For example, TNF-α inhibitors have been shown to result in the suppression of primary and secondary IgG antibody responses and cell-mediated immune function. Colagiovanni, D., et al., *Immunopharmacol.Immunotoxicol. 22*:4, 627-651 (2000). (Exhibit D). Safety alerts have been issued for commercially available TNF-α inhibitors, which are administered systemically by subcutaneous injection, due to incidents of central nervous system disorders, pancytopenia and worsening congestive heart failure. *See, e.g.,* Immunex Corporation "Dear Healthcare Professional" letter of October 10, 2000 concerning Enbrel™ [etanercept] and Centocor, Inc. "Dear Healthcare Professional" letter of October 18, 2000 concerning Remicade™ [infliximab], both available at http://www.fda.gov/medwatch. (Exhibit E). In Europe, the EMEA has warned against concurrent administration of the IL-1 receptor antagonist Kineret™ and the TNF-α inhibitor Enbrel™ due to an increased risk of serious infection and neutropenia. *EC Warns Against Concurrent Kineret and Enbrel Use*, SCRIP No. 2823, 24 (February 12, 2003). (Also included in Exhibit E). COX-2 inhibitors have been associated with an increased risk of cardiovascular events, leading to products being recalled from the market or the addition of label warnings. *FDA Information on COX-2 Selective and Non-Selective Non-Steroidal Anti-*

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

Inflammatory Drugs (NSAIDs), http://www.fda.gov/cder/drug/infopage/COX2/default.htm (July 18, 2005). (Exhibit F).

These systemically administered drugs, while having beneficial therapeutic effect, unfortunately also can be associated with incidences of serious immune, central nervous system or cardiovascular side effects in some patients. The present invention, as reflected in independent Claims 38 and 73, seeks to minimize such systemic side effects, while addressing both the inhibition of cartilage catabolism and the promotion of cartilage anabolic activity, through local delivery of the claimed compositions to the joint. In this way the desired therapeutic effect is targeted to the joint to which the composition is locally delivered, while exposure of anatomical systems and organs outside of the joint is expected to be significantly reduced. This substantial benefit of the claimed invention is not taught or suggested by the cited prior art.

D. Experimental Results in Non-prior Art References

The Office Action included an invitation for the Applicants to submit experimental data that provides a patentable distinction between the claimed methods and that of the hypothetically combined prior art references cited in the Office Action. Applicants have generated such experimental data, which is discussed below. However, to ensure due consideration, Applicants first briefly reprise experimental data establishing unexpected results from the present invention established in non-prior art references that were submitted with the last response filed by Applicants. This data was not addressed in the Office Action. If, for purposes of argument, a *prima facie* case of nonobviousness is assumed from the hypothetical combination of the cited references, and if the evidence discussed above concerning the long standing failure of those of skill in the art to recognize the present invention and the significant benefits expected to result from the local delivery methods of the claimed invention is ignored, this previously submitted

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

data alone, when appropriately considered, establishes the nonobviousness of the present invention.

The prior response demonstrated that inhibitors of cartilage catabolism have the potential to *not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to anabolic growth factors*, and thus permit repair of the damaged cartilage. This result was demonstrated by a series of recent papers published by others well after the filing of the instant priority application.

Specifically, previously submitted reference O01735 (Studer et al., *J Orthopaedic Research* 21: 914-921, 2003) demonstrated that the combination of IGF-1 (an anabolic chondroprotective agent) and the iNOS inhibitor L-NMA (an inhibitor of cartilage catabolism) stimulated proteoglycan synthesis in diseased chondrocytes while the individual agents had little to no effect on their own. Reference O01734 (Studer et al., *J Orthopaedic Research* 23: 454-461, 2005) demonstrated that TGF-β (an anabolic chondroprotective agent) and the COX-2 inhibitor SC-58125 (an inhibitor of cartilage catabolism) stimulated proteoglycan synthesis in diseased chondrocytes while the individual agents had little to no effect on their own. In addition, Studer et al. (2005) examined the effect of various combinations on the expression of TIMP-1, a factor that has positive effects on matrix homeostasis by inhibiting the matrix metalloproteinases and whose expression is suppressed by IL-1. The combination of TGF-β and the p38 MAPK inhibitor SB-203580 (an inhibitor of cartilage catabolism) induced TIMP-1 expression in IL-1 activated chondrocytes to a level that was greater than the additive effects of both agents alone, i.e., showed a *synergistic* effect, and greater than that observed in the control cultures that were not treated with IL-1. Increased levels of TIMP-1 should help restore the imbalance in matrix homeostasis that is the primary pathological feature of the osteoarthritic joint. These papers establish the effect that the evaluated inhibitors of cartilage catabolism

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

surprisingly have the potential to not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to the evaluated anabolic growth factors. This evidence constitutes the first demonstration of which Applicants are aware (other than IL-1Ra reversal of IL-1 activity) that a combination of a catabolic inhibitor and an anabolic growth factor, as claimed, has a greater positive effect on matrix homeostasis than either agent alone, which effect may be synergistic in some cases.

Taken together, the above noted non-prior art references evidence significant advantages of the present claimed invention. When locally administered with an anabolic chondroprotective agent, catabolic inhibitory chondroprotective agents not only suppress cartilage catabolic processes, but may significantly reverse the anti-anabolic effect of catabolic mediators, supporting the claimed approach for the local delivery of these combinations off agents to obtain improved cartilage protection.

E. Additional Experimental Data Showing Unexpected Results and Substantial Advantages

In still further support of the patentability of the claimed invention, and in response to the Examiner's invitation, Applicants submit additional experimental data evidencing unexpected results and substantial benefits of the presently claimed invention. This data is presented in the enclosed declaration of Emma Elizabeth (Betsy) Moore, Ph.D. (Exhibit G), who is a highly experienced scientist that currently is the Senior Group Leader in charge of the chondroprotective program at Omeros Corporation, assignee of the above-identified application. Dr. Moore directed a series of experiments evaluating inhibitors of cartilage catabolism and anabolic chondroprotective agents, as single agents and in combination, in established models of osteoarthritis using standard assays measuring markers of cartilage catabolism or cartilage synthesis. Representative reproduced (except as noted) data resulting from these experiments and experimental methods used are summarized in her declaration as Examples 1 through 4.

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

The Examiner is directed to the full text of this declaration, with the experiments performed and results obtained being only briefly summarized here to avoid redundancy. The studies described in Example 1 of Dr. Moore's declaration establish that IL-1 receptor antagonist (IL-1Ra), an inhibitor of cartilage catabolism, inhibited the degradation of cartilage matrix that is mediated by IL-1-induced proteases (e.g. MMP-13), as shown in Figure 1 of the declaration; however, it had little effect on the regeneration of cartilage matrix. Example 1 then describes studies that evaluated the effects of IL-1Ra and an anabolic factor, IGF-1, on human immortalized chondrocytes that were induced with IL-1, a model of osteoarthritis. IGF-1, a well-established anabolic agent for cartilage, could not induce matrix synthesis in these chondrocytes in the face of an IL-1 challenge. However, treating the IL-1 stimulated chondrocytes with the combination of IL-1Ra and IGF-1 restored the ability of the chondrocytes to respond to IGF-1 and synthesize increased amounts of the two major cartilage matrix components, type II collagen (Col2) and aggrecan, as shown in Figures 2, 3 and 4. The results presented in Example 1 clearly demonstrate that a locally delivered combination of a catabolic inhibitor, IL-1Ra, and an anabolic factor, IGF-1, would be expected to have a significantly greater chondroprotective effect in an osteoarthritic joint than either agent alone. IGF-1 alone would be expected to have minimal effect on the degradation of type II collagen, and it would not be able to stimulate the synthesis of cartilage matrix in the presence of elevated levels of IL-1β that are found in the osteoarthritic joint. However, local administration of IGF-1 plus IL-1Ra is expected to inhibit cartilage degradation and, surprisingly, restore the anabolic effects of IGF-1, and is thereby expected to provide the potential for repair of damaged matrix.

As described in Dr. Moore's declaration, the destruction of aggrecan in the osteoarthritic joint is attributed to increased activity of aggrecanase, which is induced by IL-1 and other cytokines. Example 2 described in Dr. Moore's declaration evaluated the effects on IL-1-

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

induced aggrecanase activity in bovine chondrocytes of the anabolic agent IGF-1 and either an Extracellular-signaling Regulated Kinase 1/2 (ERK1/2) MAPK inhibitor, U0126, or a NF-κB inhibitor, SC514, as a catabolic inhibitor. A combination of IGF-1 and the NF-κB inhibitor inhibited the IL-1-induced aggrecanase activity to 43% of the maximal response, achieving substantially greater inhibition than either agent alone (Figure 5). It was also surprising to find that IGF-1 had an effect on the aggrecanase pathway, exhibiting an anti-catabolic effect on aggrecanase activity. While less dramatic, Example 2 additionally describes similar data from evaluating IGF-1 and the ERK1/2 inhibitor in this model, with the combination achieving a greater inhibition of IL-1-induced aggrecanase activity than either agent alone (Figure 6). The data presented in Example 2 demonstrates that for the concentrations of agents used, the combination of an anabolic agent (IGF-1) and one of either two anti-catabolic agents (an ERK1/2 or NF-κB inhibitor) is more effective than any of the respective single agents in suppressing the IL-1 induction of aggrecanase activity. By extension, treatment of an osteoarthritic joint with one of these combinations of agents is expected to be more effective at inhibiting the degradation of the cartilage matrix component aggrecan than treatment with any of these agents alone.

MMP-1 is a protease that is produced by IL-1-activated chondrocytes and participates in the degradation of cartilage matrix components type II collagen and aggrecan. Example 3 described in Dr. Moore's declaration evaluated the effect of IGF-1 and either the p38 MAPK inhibitor SB239063 or the NF-κB inhibitor SC514 on the suppression of IL-1 induction of MMP-1 mRNA The data presented in this example demonstrates that for the concentrations of agents used, the combination of an anabolic agent (IGF-1) and either a p38 MAPK inhibitor (Figure 8) or a NF-κB inhibitor (Figure 9) is more effective than any of the respective single agents in suppressing the IL-1 induction of MMP-1 mRNA. By extension, treatment of an osteoarthritic joint with the combination of IGF-1 plus the tested p38 MAPK inhibitor or IGF-1

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

plus the tested NF-κB inhibitor should be more effective at inhibiting matrix degradation than treatment with any of these agents alone.

MMP-13 is thought to be one of the major proteases involved in the degradation of type II collagen in the osteoarthritic joint. Any agent that blocks its production and/or activity should have a beneficial effect in the osteoarthritic joint. In Example 4 of Dr. Moore's declaration, it is shown that IL-1β/TNFα induction of proMMP-13 in an immortalized human chondrocyte cell line was inhibited in a concentration-dependent manner by inhibitors of the p38 MAPK signal transduction pathway. In addition, it was shown that saturating concentrations of Bone Morphogenetic Protein-2 (BMP-2) and BMP-7, which are anabolic chondroprotective agents, partially inhibited proMMP-13 induction. (Figures 10-12). The presence of BMP-2 or BMP-7 reduced the amount of p38 MAPK inhibitor that was required for complete inhibition by an order of magnitude. The clinical development of p38 inhibitors for treatment of inflammatory conditions has been complicated by toxic side effects of these agents on cell types other than the intended target. Therefore, the finding that the combination of BMP-2 or BMP-7 and a p38 inhibitor would require ten-fold lower levels of the p38 inhibitor for maximal inhibition of proMMP-13 production by the chondrocytes in an osteoarthritic joint demonstrates the superiority of the combination compared to either agent alone. The local delivery of such combinations in accordance with the claimed methods of the present invention further reduce the potential for toxic side effects.

Taken together, the experimental data set forth in the previously submitted non-prior art references and in the enclosed declaration of Dr. Moore establish that the present invention provides substantial benefits over the prior art and surprising and unexpected results. It is respectfully submitted that the rejection under 35 USC § 103 should be withdrawn.

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

V. Closure

Applicants have submitted substantial evidence establishing that the pending claims are fully enabled and patentably nonobvious. In view of the above remarks, reconsideration and passage of each of claims 38-60 and 73-81 to issue is respectfully requested. Should the Examiner have any remaining questions or concerns, he is invited to telephone the undersigned attorney.

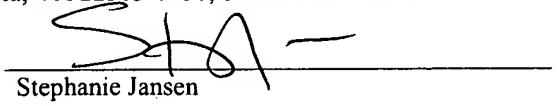
Respectfully Submitted,

OMEROS CORPORATION

Marcia S. Kelbon
Vice President, Patent & General Counsel
Registration No. 34,358
Direct Dial No. 206.676.5020

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

11-6-06
Date



Stephanie Jansen

MSK:sj

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688